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(19)

(54) EYE OINTMENT

(71) We, FISONS LIMITED, a British Company of Fison House, 9 Grosvenor Street, London W.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel pharmaceutical composition.

According to our invention we provide a sterile ointment, suitable for use in the eye, especially the human eye, comprising, as active ingredient, 1,3 - bis(2 - carboxychromon - 5 - yloxy)propan - 2 - ol, 1,3 - bis(2 - carboxychromon - 7 - yloxy)propan - 2 - ol, or a pharmaceutically acceptable (e.g. the di - sodium) salt of either in a base comprising one or more of glycerol, waxes, fats, proteins, paraffins, or polyalkylene glycols.

Such compounds are described and claimed in our U.K. Patent No. 1,144,905.

Where the base comprises a wax, the wax is preferably a hard or soft paraffin wax, e.g. hard paraffin BP or white soft paraffin BP; where it comprises a fat, the fat is preferably wool fat; where it comprises a protein, the protein is preferably gelatin; where it comprises a paraffin, the paraffin is preferably a liquid paraffin, e.g. liquid paraffin BP; and where it comprises a polyalkylene glycol, the polyalkylene glycol is preferably polyethylene glycol.

The ointment may also contain other liquid components, e.g. water, in an amount of from 1 to 10% w/w, to improve the consistency of the base, provide a solvent for the active ingredient so that the active ingredient may be sterilised by filtration and/or to alter the rate of release of the active ingredient from the base.

The composition may if desired contain an effective proportion of a pharmaceutically acceptable preservative or sterilising agent suitable for an ointment. Examples of preservatives which may be used are (i) Chlorbutol (2,2,2 - trichloro - 1,1 - dimethyl ethanol hemihydrate), which may be present in the composition at 0.1 to 1.0%, e.g. about 0.5% w/w, (ii) Chlorocresol, which may be present in the composition from 0.05% to 0.2% w/w and, (iii) methyl - p - hydroxybenzoate, either alone or in combination with propyl - p - hydroxybenzoate. The total concentration of hydroxybenzoate esters in the composition may range from 0.08% to 0.2% w/w.

We prefer to use a composition containing a major proportion (e.g. 70—90% w/w) of a white or yellow soft paraffin and minor proportions of a liquid paraffin (5—15% w/w) and of a hard paraffin (0—12% w/w).

We also prefer to use a composition containing from 0.5 to 10% and preferably from 2 to 6% w/w of active ingredient.

The active ingredient is preferably used in micronised form, e.g. having a mean particle size in the range 0.01 to 10 microns.

Conventional thickening agents, e.g. gelatin, pectin, zinc oxide, starch, bentonite and cellulose derivatives, e.g. carboxymethyl cellulose, are desirably absent from the present compositions.

The composition may be made conventionally. Thus, typically, the active ingredient is micronised, and sterilised by heating, e.g. at 160°C for not less than one hour. The paraffins are melted, passed through a 200 mesh screen, and sterilised in the same manner. The paraffin base is cooled to 70°C, and a small portion of the base is withdrawn and the sterilised active ingredient is dispersed in this portion. The remainder of the base is added in small portions, and the whole stirred until ambient temperature is reached. All operations are performed aseptically in a sterile area.

Alternatively, and especially if the active ingredient is not stable to heat, it may be dissolved in the minimum quantity of hot purified water, the solution sterile filtered, and mixed aseptically with the melted paraffin base.

According to our invention we also provide a method of treatment of conditions of the eye in a non-human animal in which conditions allergy or immune reactions play at

least a contributory part, which method comprises administration of an ointment of the present invention to the eye of the animal having such a condition.

The dosage to be administered will of course vary with the condition to be treated, with its severity and with the patient concerned. We have found that the ointments of the present invention release the active ingredient to the eye in a controlled manner, and at a slower rate than corresponding solutions thereof. A dosage of 0.5 to 4.0 mg of active ingredient into the affected eye from 1 to 4 times, and preferably twice, a day is found to be generally satisfactory. More frequent dosage may be used if desired.

Conditions of the outer eye in which the method of the invention is indicated include vernal catarrh (vernal kerato-conjunctivitis) and marginal corneal ulceration or infiltration. Other conditions which may be treated by the method of the invention include the ocular effects of hay fever, 'allergic eyes' where the allergen is known or unknown and springsummer conjunctivitis. This latter term is used to mean allergic disorders of the eyes occurring in the spring and summer where an external allergen plays a part in the disorder. Further conditions of the eye which may be mentioned are 'irritable eye' or 'non-specific conjunctivitis', Herpes Simplex Keratitis and Conjunctivitis, Herpes Zoster Keratitis and Conjunctivitis, adenovirus infections, phlyctenular conjunctivitis, corneal homograft rejection, Trachoma, antirioruveitis and drug sensitivity.

The invention is further described, though only by way of illustration, in the following Examples.

Example 1

Disodium salt of 1,3 - bis-(2 - carboxychromon - 5 - yloxy)propan - 2 - ol	4.0% w/w
White soft paraffin BP	81.0% w/w
Liquid paraffin BP	10.0% w/w
Hard paraffin BP	5.0% w/w

The composition was made up by the procedure first described above.

Example 2

Disodium salt of 1,3 - bis-(2 - carboxychromon - 5 - yloxy)propan - 2 - ol	4.0% w/w
Purified water	q.s.
Base to	100% w/w
Base:	
Polyethylene glycol 400	5.0% w/w
White soft paraffin BP	80.0% w/w
Liquid paraffin BP	10.0% w/w
Hard paraffin BP	5.0% w/w

The composition was made up by the procedure described above in which the active ingredient was first dissolved in the minimum quantity of hot purified water.

Example 3

Disodium salt of 1,3 - bis-(2 - carboxy - 7 - yloxy)-propan - 2 - ol	4.0% w/w
White Soft paraffin BP	81.0% w/w
Liquid paraffin BP	10.0% w/w
Hard paraffin BP	5.0% w/w

The composition was made up by the procedure first described above.

Example 4

The ointments of Examples 1, 2 and 3 were applied with good results to the eyes of human patients suffering from vernal kerato-conjunctivitis.

WHAT WE CLAIM IS:—

1. A sterile ointment, suitable for use in the eye, which comprises, as active ingredient, 1,3 - bis(2 - carboxychromon - 5 - yloxy)-propan - 2 - ol, 1,3 - bis(2 - carboxy-chromon - 7 - yloxy)propan - 2 - ol, or a pharmaceutically acceptable salt thereof, in a base comprising one or more of glycerol, waxes, fats, proteins, paraffins, or polyalkylene glycols.

2. An ointment as claimed in claim 1 wherein the active ingredient is present as the disodium salt.

3. An ointment as claimed in claim 1 or claim 2, wherein the active ingredient is present in an amount of from 0.5 to 10% w/w.

4. An ointment as claimed in claim 3, wherein the active ingredient is present in an amount of from 2 to 6% w/w.

5. An ointment as claimed in any of claims 1 to 4 wherein the active ingredient has a mean particle size in the range 0.01 to 10 microns.

6. An ointment as claimed in any of claims 1 to 5 wherein the base comprises one or more of hard paraffin waxes, wool fat, glycerol, gelatin, liquid paraffins and polyethylene glycol.

7. An ointment as claimed in claim 6, wherein the base comprises from 70 to 90% w/w of a white or yellow soft paraffin, from 5 to 15% w/w of a liquid paraffin and 0 to 12% w/w of a hard paraffin.

8. An ointment as claimed in any of claims 1 to 7 which contains water in an amount of from 1 to 10% by weight.

9. An ointment as claimed in any of claims 1 to 8 which contains one or more suitable pharmaceutically acceptable preservatives or sterilising agents.

10. An ointment as claimed in any of claims 1 to 9 substantially as described herein in any one of the Examples.

11. A method for the treatment of conditions of the eye of a non-human animal in which conditions allergy or immune reactions play at least a contributory part, which method comprises administration of an ointment as claimed in any of claims 1 to 10 to the eye of the animal having such a condition.

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